Current Concepts of Cancer Chemotherapy

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• **The most impressive regressions obtained to date with the use of chemotherapy are in metastatic choriocarcinoma of females. In the management of Hodgkin's disease, leukemia, and lymphoma, chemotherapy is a useful and accepted form of therapy. In many cases radiation and chemotherapy are interdependent. In disseminated carcinomas arising in the lung, ovary or breast, there is less likelihood of significant improvement with the use of chemotherapy, but if the disease is not amenable to radiotherapy, useful palliation can be obtained at times.**

While newer chemotherapeutic agents for cancer, notably the pyrimidine analogues, have a broader spectrum of antitumor effects than others investigated earlier, they should be regarded as providing a valuable research stimulus in the continued search for more effective and less toxic agents.

FOLLOWING World War II the introduction of the nitrogen mustards into clinical cancer chemotherapy initiated a new era in the treatment of cancer. Extensive efforts to find chemical means of controlling neoplastic disease ensued, and the valid role of chemotherapy in medical practice remains poorly defined in many areas. In an attempt to clarify the relative role of present day chemotherapy, we propose to review briefly the types of agents known to be beneficial and the conditions in which they may be useful.

ALKYLATING AGENTS

Alkylating agents are substances which under physiological conditions are capable of reacting selectively with desoxyribonucleic acid (DNA) so that cellular injury results. The prototype of this group of substances is nitrogen mustard, although hundreds of other kinds of alkylating agents have been synthesized in the attempt to increase the therapeutic efficacy and lessen the toxicity of this compound. Structural variations include the beta chloroethyl group, the ethyleneimines and the methane sulphonyloxy alkanes (Figure 1). With all these compounds, the biological activity and clinical effectiveness are remarkably consistent. The only exception is busulfan (Myleran®), 1:4-dimethanesulphonyloxybutane, which unlike other alkylating compounds, preferentially depresses granulopoiesis rather than lymphopoiesis, so that this is a most effective agent in the management of chronic granulocytic leukemia.[33] Freedom from gastrointestinal side effects has made some agents such as chlorambucil and triethylene melamine very useful in clinical practice, but therapeutic superiority has not been demonstrated. Comparative studies suggest that thiotriethylene phosphoramide (TEPA) is slightly inferior therapeutically to nitrogen mustard in several diseases.[40]

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Submitted February 21, 1962.

CLINICAL USE

The preliminary report of the clinical use of the nitrogen mustards by Rhoads[32] in 1946 indicated that their therapeutic value was the induction of temporary regression in certain malignant diseases, namely Hodgkin's disease, lymphosarcoma, chronic lymphocytic leukemia, chronic granulocytic leukemia and polycythemia vera.[32] Subsequent studies were indicative of transient antitumor effects in some patients with carcinoma of the lung, carcinoma of the breast, carcinoma of the ovary, carcinoma of the nasopharynx, carcinoma of the cervix, seminoma, malignant melanoma, choriocarcinoma of females, neurogenic sarcoma and neuroblastoma.[21,22] In acute leukemia reduction of the number of leukocytes in peripheral blood, with disappearance of fever, was noted, but no remission of the disease.[5]

Hodgkin's disease. It is in the management of disseminated Hodgkin's disease that the nitrogen mustards have been most effective.[11,14] Reduction of enlarged lymph nodes, diminished hepatosplenomegaly, relief of bone pain and subsidence of fever, sweats, pruritus and anemia may occur. The primary

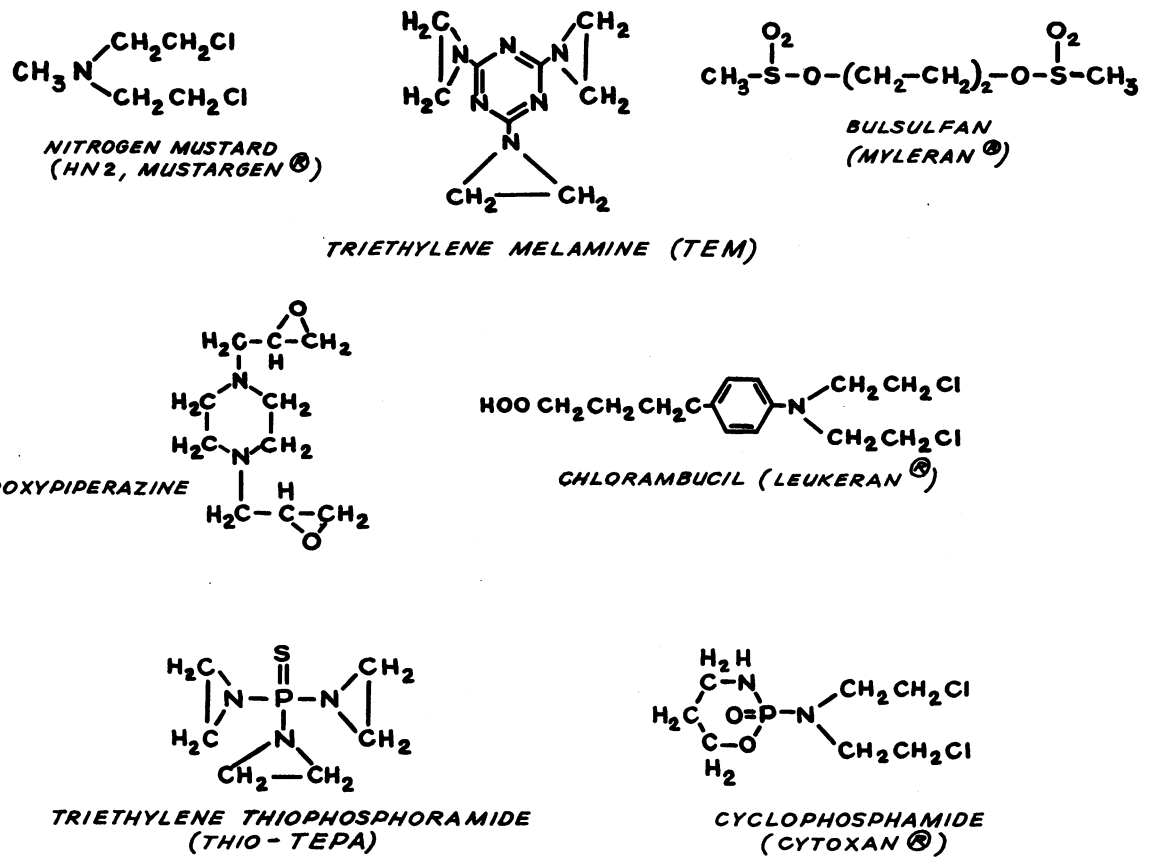

Figure 1.—Structural variations in alkylating agents.

consideration for the use of nitrogen mustard is evidence of disseminated disease, since it is apparent that clinically localized disease may be maintained in remission of many year's duration following aggressive radiotherapy.[31] The use of suppressive oral alkylating agents may significantly prolong the remission achieved by nitrogen mustard, but this method of treatment requires meticulous attention to the peripheral blood lest permanent bone marrow hypoplasia result.

Malignant lymphoma. In the management of malignant lymphoma the qualitative results achieved are much like those observed in Hodgkin's disease, but the response is less predictable. In patients with slowly progressive disease, a gradual prolonged remission may follow nitrogen mustard treatment. Those with aggressive disease may obtain a rapid transient response.

Chronic leukemia. Alkylating agents are capable of successfully reducing and controlling the peripheral blood count in patients with chronic leukemias, as well as producing a rise in hemoglobin levels, diminution of hepatosplenomegaly and general improvement in clinical status. Because of the ease of administration and low toxicity, oral alkylating agents such as chlorambucil and triethylene melamine (TEM) have been the conventional forms of chemotherapy in chronic lymphocytic leukemia. The indications for therapy are largely dependent upon the clinical manifestations of the disease, since lymphocytic proliferation is random and the number of lymphocytes in the peripheral blood does not parallel the manifestations of the disease.[9] In chronic granulocytic leukemia, the symptoms of the disease generally correlate with the proliferative activity of the leukocytes, so that the rate of leukocyte increase is a useful guide in initiating treatment. Busulfan (Myleran) will induce hepatopoietic and clinical improvement in most cases.[10]

Carcinoma. Although genuine benefit may follow treatment with alkylating agents in several types of carcinoma, the majority of these tumors are unresponsive. Nitrogen mustard treatment is effective in 20 to 70 per cent of cases of bronchogenic carcinoma, the variation depending upon cell type, the oat cell or undifferentiated cell types being the most responsive.[2,23,25] Prompt relief of superior vena caval obstruction, reduction of pleural effusion, regression of primary and metastatic lesions, and

general symptomatic improvement may result. The duration of the response is generally brief, rarely exceeding six months. A recent study demonstrated that some increase in survival can be achieved by nitrogen mustard treatment in patients with bronchogenic carcinoma.[38]

In the management of carcinoma of the breast that is refractory to hormonal or endocrine ablative procedures, alkylating agents may induce regression in 10 to 20 per cent of cases.[40] The high incidence of improvement achieved by Bateman with Thio TEPA (triethylene thiophosphoramide) was not achieved by Moore, Olson, Ultmann or Wright.[1,29,30,37,39]

In ovarian carcinoma, alkylating agents may induce symptomatic improvement in 25 to 50 per cent of cases, as manifest by diminution of ascites, reduction of tumor masses, relief of ureteral or intestinal obstruction.[28,35]

Miscellaneous neoplasms. Alkylating agents may be used in other neoplastic diseases such as malignant melanoma, neuroblastoma, seminoma and carcinoma of the cervix depending upon the stage of the disease and the clinical situation. The results are less predictable than in the conditions already mentioned, but if progressive disseminated disease is present and the general condition of the patient is good, an empiric trial is reasonable.

ANTIMETABOLITES

Cancer chemotherapy with antimetabolites has developed as the result of attempts directed toward inducing selective deficiencies of metabolites essential for nucleic acid synthesis. Their effectiveness depends upon preferentially affecting the growth rate of the tumor to an extent greater than that of normal tissue. The classes of antimetabolites in current use are the folic acid antagonists, purine antagonists and, more recently, pyrimidine analogues. Folic acid antagonists exert their effect on nucleic acid formation by reducing the source of single carbon fragments for purine, pyrimidine and amino acid synthesis.[13] Purine antagonists are less specific in their mode of action but interfere with nucleotide synthesis.[34] Certain pyrimidine analogues are incorporated into macromolecules, disrupting function of nucleic acids as well as interfering with their synthesis.[6]

Amethopterin

Amethopterin or methotrexate is the folic acid antagonist in widest use, its clinical use being greatest in the treatment of acute leukemia in childhood. Eight years following the first clinical trials, Li and Hertz reported successful treatment of choriocarcinoma of females with this agent.[26] Recent reports indicate complete regression can be achieved in about half the cases.[17] Some cases of mycosis fungoides and squamous carcinoma of the head and neck will show regression following the use of high doses of amethopterin.

6-Mercaptopurine

6-mercaptopurine, an adenine analogue, is used primarily in the treatment of acute leukemia of adults. A remission rate of 10 to 20 per cent may be obtained.[4] It is effective in the treatment of chronic granulocytic leukemia as well, but busulfan is generally used, the antimetabolite being reserved for use in the event of a terminal acute phase of the disease.

5-Fluorouracil

5-fluorouracil, a pyrimidine analogue, has shown a wide spectrum of antitumor effect in human neoplastic diseases, the most decided responses being reported in patients with carcinoma of the breast and carcinoma of the colon.[7,12] In general, the responses are brief and the proportion of cases reported responding has varied from 10 per cent to 40 per cent. The drug has a narrow therapeutic range and in effective doses generally produces significant and often serious toxic effects.[12] Since the incidence of responses is low and generally unpredictable, other conventional types of chemotherapy are preferable in such diseases as carcinoma of the breast and ovary. In the treatment of carcinomas arising in the gastrointestinal tract, the use of this drug is best considered as investigative rather than conventional chemotherapy.[41]

Pyrimidine nucleosides

The introduction of the pyrimidine nucleosides, 5-fluoro-2'desoxyuridine (5-FUDR) and 5-iodo-2-desoxyuridine (5-FIDR) represents additional efforts directed toward interference with pyrimidine biosynthesis. 5-FUDR shows greater localization in tumor tissue and less toxicity in animals than does 5-fluorouracil.[16] Clinical studies suggest less toxicity as well, so that potentially clinically more useful pyrimidine analogues may be forthcoming.

MISCELLANEOUS AGENTS

While many agents have received clinical trial, few are of current interest.

Vinblastine

Vinblastine is an extract of periwinkle plant reported to induce regression in some patients with Hodgkin's disease, lymphoma, carcinomas of the breast and colon, acute leukemia and choriocarcinoma of females.[18,19] The side effects include bone marrow depression, anorexia, nausea and central

nervous system disturbances. Its clinical role is yet to be determined.

Actinomycin D

The antibiotic actinomycin D is capable of producing regression in some tumors of embryonic origin, namely Wilm's tumor and rhabdomyosarcoma, with regression as well in some cases of lymphosarcoma, Hodgkin's disease, melanoma, epidermoid tumors, neuroblastoma and carcinoma of the gastrointestinal tract.[36] It is also capable of inducing a fall in the gonadotropin titer in patients with testicular carcinomas, so that it has been used in the combination therapy (with other chemotherapeutic agents) of that disease.[27] On the whole, the incidence of tumor response in any of the above mentioned diseases is small and the side effects are usually significant, so that it has no substantial role in clinical chemotherapy.

Demecolcin

This derivative of colchicine has one-thirtieth the toxicity of the parent compound, and has been used in the treatment of chronic granulocytic leukemia.[24] It is capable of inducing remission in the majority of cases. Current studies are in progress to ascertain whether it is superior to busulfan in that disease.

op'DDD

op'DDD (2,2-bis 4-chlorophenyl, 2 chlorophenyl) -1-1-dichlorethane) an analogue of DDT, the insecticide, has been observed to have a selective destructive effect upon the adrenal cortex. Its use in patients with adrenal carcinoma reveals tumor regression as well as steroid suppression.[3] The lack of hazardous side effects suggests that this is a potentially useful agent.

COMBINATION THERAPY

The possibility of potentiating the effectiveness of agents by using them in combination with radiotherapy has stimulated numerous such clinical trials. Alkylating agents, actinomycin D and 5-fluorouracil are the agents in most frequent use in combination.

Alkylating agents with irradiation

In patients with superior vena caval obstruction, spinal cord compression, respiratory distress or ureteral obstruction, the prompt relief that may follow nitrogen mustard treatment makes it desirable as initial therapy in these situations—particularly in Hodgkin's disease, lymphoma, bronchogenic and ovarian carcinomas. Subsequent use of radiotherapy may satisfactorily control the disease. However, in localized Hodgkin's disease, nitrogen mustard therapy before radiation in the attempt for "curative" treatment is without proved value.

In the treatment of retinoblastoma, the combination of an alkylating agent, triethylene melamine (TEM) with radiation appeared to offer therapeutic advantage compared with the use of radiation alone.[20] However, the use of TEM alone or lower dose radiation alone has not yet been assayed.

Actinomycin D with irradiation

Since actinomycin D accentuates the skin reaction of radiation, it has been used in combination, particularly in the treatment of Wilms' tumor.[8] While the response rate is greater with the use of the combination than with the use of the drug alone, a concomitant evaluation of adequate radiotherapy is lacking.

5-Fluorouracil with irradiation

Reports of the potentiation of antitumor effect when 2000 r is given in conjunction with 5-fluorouracil have led to the use of this combination.[15] The largest number of cases were of bronchogenic carcinoma; others included tumors responsive to either 5-fluorouracil or irradiation singly. In the bronchogenic tumors, it is quite likely that anaplastic tumors would show significant regression with the use of 2000 r alone. Although an occasional case may show a seemingly good response from this type of combination therapy, the duration of the effect as compared with that of controls, in our experience, is not clearly greater than that obtained with either agent alone. Thus, the demonstration of adequate evidence of potentiation would require a properly designed controlled investigation in which many cases are included.

The broad spectrum of clinical behavior, responsiveness, and survival in human neoplastic diseases necessitates careful controlled studies of drug and radiation effect singly so that the results of combination therapy can be properly assessed. Highly sensitive tumors will regress with lesser doses of either therapeutic modality.

DISCUSSION

Relatively few neoplastic diseases are managed solely by chemotherapy. The concept of ultimate chemical control of cancer, although enticing, challenging, and worthy of intense research effort, is one which at this time remains visionary for most types of cancer. The broad spectrum of types and behavior of human malignant disease suggests that a diversity of agents may be required in much the same way that various antibiotics are needed in the treatment of bacterial diseases.

Few aspects of medical science are associated with reports so extravagant and enthusiastic as those stimulated by new anticancer chemotherapeutic agents. Assessment is sometimes hampered by

optimistic claims which cannot be confirmed, so that progress is limited by repeated evaluations.

Since chemotherapeutic agents exert their effects on proliferating tissue, normal tissues are regularly affected. For this reason, chemotherapeutic agents should not be considered as innocuous and should not be administered indiscriminately. Some agents such as 5-fluorouracil have an equivalent opportunity of inducing either some benefit or severe toxicity just short of a fatal outcome.[41]

In order to develop substances free of toxic effects on normal tissue, the factors by which neoplastic growth differs from normal growth require further elucidation. This is a goal for the future, and for some time to come progress will continue along present day empiric approaches.

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